

REMARKS

The Official Action of October 1, 2002, and the prior art relied upon therein have been carefully reviewed. The claims in the application are now claims 1, 2, 6-14, 16 and 18, and these claims define patentable subject matter warranting their allowance. Applicant accordingly respectfully requests favorable reconsideration and allowance.

Acknowledgement by the PTO of the receipt of applicant's papers filed under §119 is noted.

Before addressing the rejections, applicant would like to review the present invention. The starting point of the present invention is the applied Cynshi et al disclosure (hereinafter "Cynshi") which describes active compounds used in the present invention and the utility of such compounds. However, applicant was faced with certain problems which are inherent in Cynshi, but are not addressed in Cynshi, namely the problems of stability of the active compounds and their absorbability when administered to a patient. No hint is given in the prior art as to how to improve stability and absorbability.

Cynshi broadly discloses various dosage forms at column 5 commencing at line 33, including "capsules" and "solutions". As regards oral administration, suspensions are

mentioned in test examples 4 and 5, i.e. suspension of the active compound in a 1% carboxymethyl cellulose solution (column 13, lines 4-50; column 14, lines 37-39).

Thus, there is nothing in Cynshi leading toward the present invention. Moreover, as will be addressed more fully below in reply to the prior art rejections, the other prior art relied upon by the PTO also does not lead the person of ordinary skill in the art to any solution to the problems faced by the applicant, i.e. particularly improving stability. The applicant has solved such problem by dissolving the active compound in soybean oil which "is especially preferred" (applicant's specification, page 5, line 23). As regards the effects produced, the final sentence of test example 1 (page 13, lines 4 and 5) states as follows:

Relatively high stability was observed in the case where soybean oil was used.

And, with respect to increasing absorbability, please see the last sentence of test example 2 (page 14, lines 11-14):

Sample 1 in which soybean oil was used as solvent showed the highest plasma level shift and the AUC value for sample 1 was about 4 time and about twice as high as compared with those for samples 2 and 3, respectively.

Thus, the present applicant has discovered that a soft capsule containing the active compound and soybean oil has increased

stability of the active compound, and when administered results in increased absorbability.

New claim 18 has been added. Support is found in claim 1 and the examples, as well as in the text quoted above. Claim 18 is patentable for the same reasons as the other claims, as pointed out above and below.

Claims 1-14 and 16 have been rejected under the second paragraph of §112. The rejection is respectfully traversed.

Applicant has no idea why the word "general" would change something which is quite specific, as defined by the formula, into something which is indefinite. Applicant respectfully disagrees that the word "general" in any way makes the claims indefinite, and respectfully points out that there are thousands of U.S. patents, many recently issued, having claims including the language "general formula". Applicant believes that the claims as originally drafted, even without being considered in light of applicant's specification (consistent with the law), would not have been confusing to those skilled in the art, and therefore the claims in their previous form are fully in accordance with the second paragraph of §112. At **worst**, the language "general formula" might be considered objectionable, but **only** as to form.

Nevertheless, in deference to the examiner's views and to minimize needless argument, the term "general" has been deleted. Such an amendment is clearly of a formal nature only, and is in no way a "narrowing" amendment because the scope of the claims has not been reduced in this regard.

Applicant respectfully requests withdrawal of the rejection.

Claims 1-17 have been rejected as obvious under §103 from Borkan et al USP 4,935,243 (Borkan) in view of Cynshi. This rejection is respectfully traversed.

As indicated above, the present invention is based on the discovery that the dihydrobenzofuran derivative of formula (1) set out in claim 1, which is susceptible to oxidation, not only remains stable without any antioxidant but also exhibits a high capability of being absorbed by the body when it is dissolved in soybean oil. The enhancement of the stability and the absorption by soybean oil is shown in Figs. 1 and 2, respectively.

Borkan suggests, among many other possibilities, that a soft capsule fill material can be prepared by dissolving one or more biologically-active compounds in a vegetable oil such as corn oil, peanut oil, safflower oil, sunflower oil, or soybean oil. However, it is silent on the combination of a biologically-active compound with soybean oil

which results in the enhancement of the stability and the absorption of the compound by soybean oil. This is because Borkan is directed to only rendering a soft capsule shell dispersible and soluble in the mouth of a user by including a hydrogentated starch hydrolysate in the shell. See column 3, lines 9-18 and column 4, lines 6-9.

Moreover, Borkan does not focus on soybean oil, or indeed any particular fill material which, as stated at column 5, lines 43-45, can be any one of liquid, semi-solid, solid, or gel. Thus, Borkan provides only an immense "shotgun" or "basket" disclosure of possibilities, and really directs the person of ordinary skill in the art in no particular direction. The choices are extremely great, and picking any particular fill material is basically akin to figuring out the combination of a safe merely by looking at the dial.

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Moreover, as indicated above, the focus in Cynshi is to provide a chewable capsule, and therefore taste and mouth solubility are paramount, factors which again do not lead the person of ordinary skill in the art toward the present invention. And of course the most important point, also emphasized above, is the total absence in Borkan of providing any motive or incentive for solving the problems relating to stability and absorbability, or even to mention any active compound which suffers any stability problem.

Cynshi does not make up for the deficiencies of Borkan as noted above. Thus, as discussed above, Cynshi is also silent on the enhancement of the stability and the absorption of the dihydrobenzofuran derivative disclosed therein by soybean oil.

It therefore follows that a consideration of Borkan together with Cynshi by the person of ordinary skill in the art, seeking to solve the problems faced by applicant, i.e. the problems of stability and absorbability, would not have found any solutions to those problems, as the prior art provides no hint as regards such problems, let alone their solution.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 1-17 have also been rejected as obvious under §103 from Borkan in view of Cynshi, and further in view of DeMichele et al USP 6,013,665 (DeMichele). This rejection is respectfully traversed.

Borkan and Cynshi have been discussed above, and applicant's comments made above with respect to these two citations are respectfully repeated by reference.

DeMichele discloses a method for enhancing the absorption of lipophilic compounds in an animal comprising administering to the animal: (a) at least one lipophilic

compound in conjunction with (b) a structured glyceride component containing a long chain triglyceride (LCT) and a medium chain triglyceride (MCT) in a certain proportion. See column 3, line 65 to column 4, line 6. In DeMichele, soybean oil is described as a source of LCT. See column 6, lines 24-38. This suggests that soybean oil by itself would not be able to enhance the absorption of lipophilic compound. DeMichele is silent on the enhancement of the stability of the lipophilic compound by soybean oil.

A consideration of DeMichele alone or DeMichele together with Cynshi and Borkan would not have given the person of ordinary skill in the art any expectation that soybean oil by itself would provide superior absorbability compared with other vegetable oils, or that it would improve the stability of an active compound which is susceptible to oxidation. Applicant's invention would not have been obvious from a consideration of the citations together.

In short, none of the references either discloses or suggests that soybean oil would be able to enhance both the stability and the absorption of even the compounds disclosed in these citations. Therefore, one of ordinary skill in the art would not have been motivated from the reference to make the claimed soft capsule formulation with the expectation that soybean oil would enhance both the stability and the

absorption of the claimed dihydrobenzofuran derivative of formula (1).

Withdrawal of the rejection is in order and is respectfully requested.

Applicant respectfully requests favorable reconsideration and allowance.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By



Sheridan Neimark

Registration No. 20,520

SN:jaa

Telephone No.: (202) 628-5197

Facsimile No.: (202) 737-3528

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